New Series Volume 1 Number 6



*The American Journal of*

# DIGESTIVE DISEASES

*June 1956*



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# DIGESTIVE DISEASES

THE AMERICAN JOURNAL OF DIGESTIVE DISEASES is a clinical journal edited primarily for physicians and surgeons engaged in active practice and concerned directly with diagnosis and care of patients. It is devoted to prompt publication and dissemination of soundly based investigation and clinical study in the field of Gastroenterology broadly defined. The Journal includes within its scope the practical aspects of diseases of the digestive system, including nutritional and metabolic disturbances and diseases of the liver.

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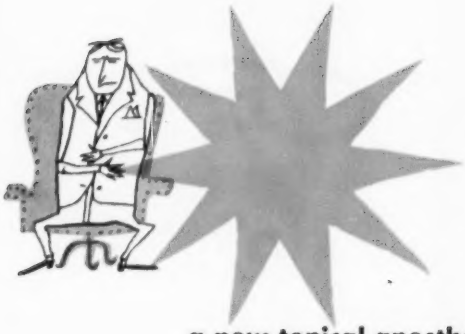

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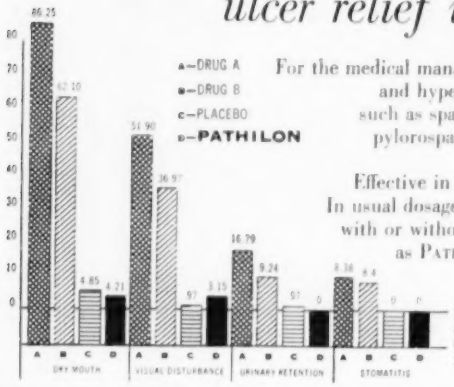


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1. "Evaluation of Drugs in the Treatment of Peptic Ulcer" by J. M. Ruffin, M. D.; D. Cayer, M. D.; J. S. Atwater, M. D., and B. G. Oren, M. D., Exhibit at A.M.A. Meeting, Atlantic City, June, 1955.
2. J.A.M.A. 160:389 (Feb. 4) 1956.

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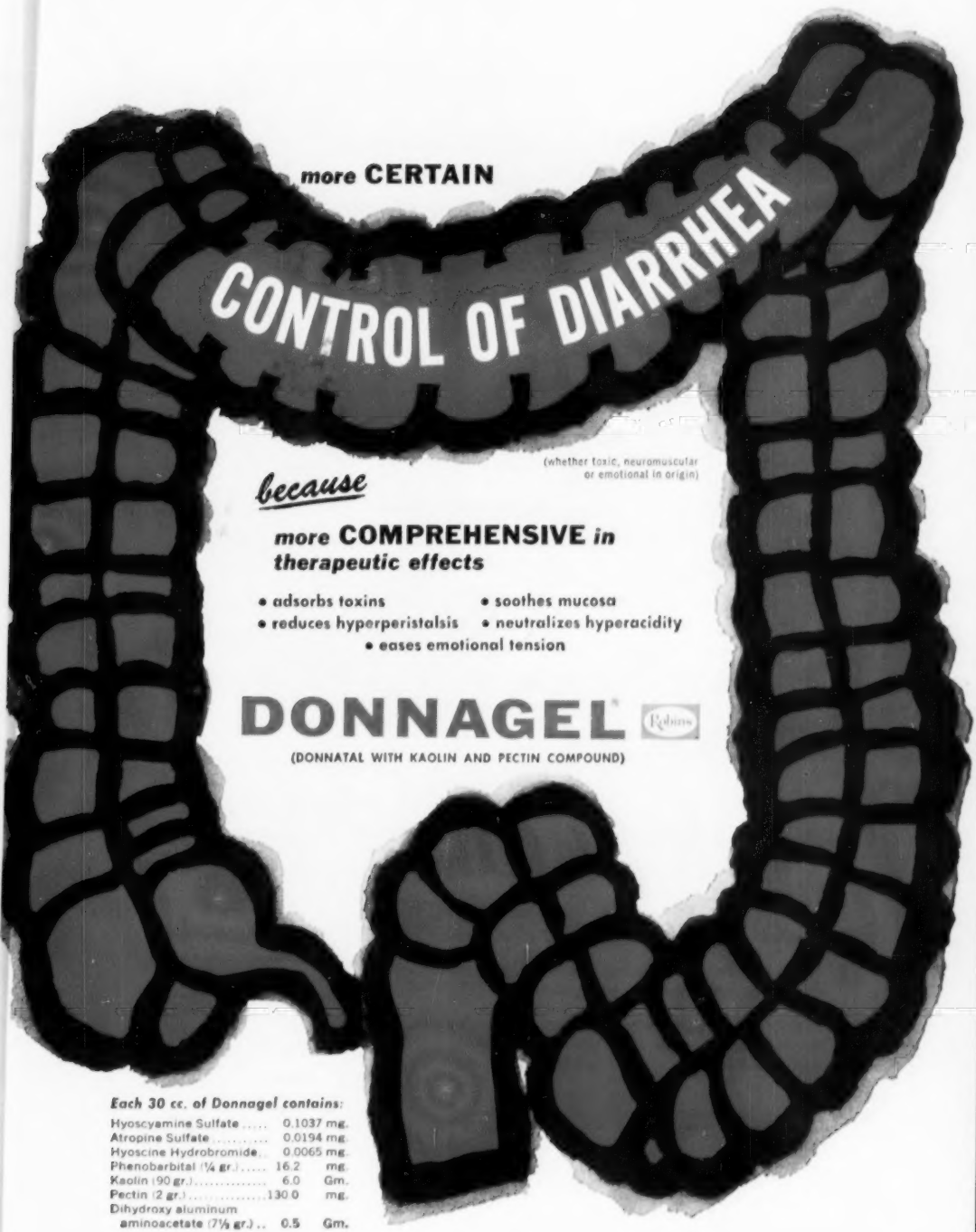


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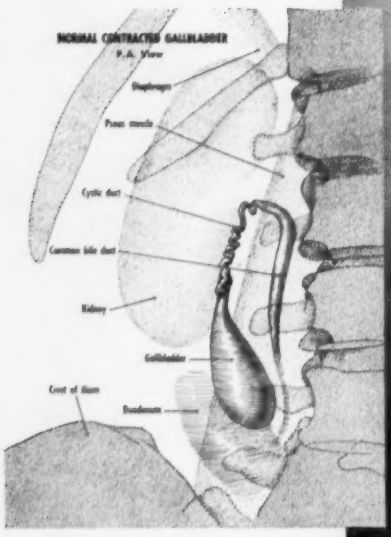


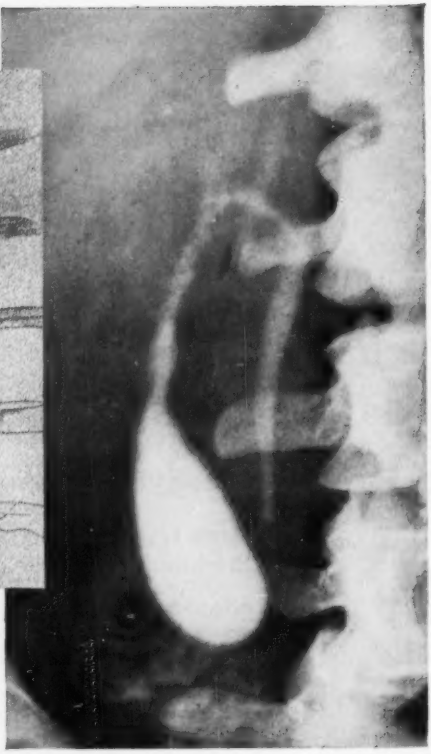

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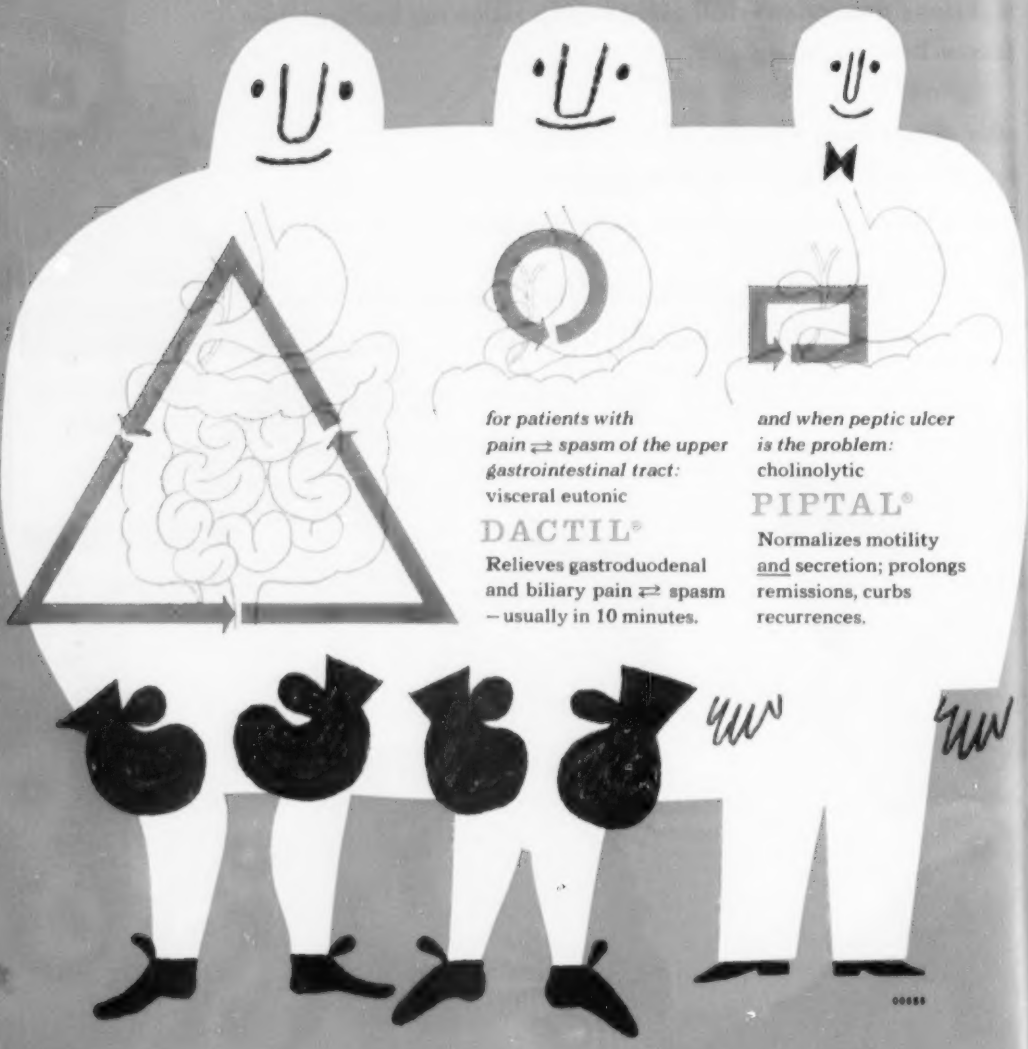

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# *Tubeless Gastric Analysis*

## Evaluation of a Technic Using a Dye–resin Compound

MAURICE L. SIEVERS, M.D.,* and RALPH V. GIESELMAN, M.D.

THE DEVELOPMENT by Segal and coworkers in 1950 of certain cation-exchange resins[1] made it clinically possible to estimate the ability of the stomach to secrete hydrochloric acid without intubation. Numerous studies[2-12] have been published since then regarding the efficacy of a quininium cation-exchange resin for tubeless gastric analysis. Although qualitatively accurate, the tubeless method is definitely quantitatively inferior to intubation. However, a simpler technic to detect inability of the stomach to secrete free hydrochloric acid is desirable Such a feature would be advantageous, for example, in mass screening for gastric malignancy. Previous experience with intubation gastric analysis as a screening device in cancer of the stomach has been encouraging.[13, 14]

Segal has reported a new cation-exchange resin for the tubeless test in which a dye (azure A), instead of quinine, is coupled to the resin amberlite XE-96.[15, 16] As with the older quininium compound, Diagnex, hydrogen ion exchanges with the indicator substance. The released indicator is then absorbed from the gastrointestinal tract and excreted in the urine. The principal advantage of the dye–resin compound over the quininium substance is that results are obtained by a simple, rapid colorimetric test on the urine without the use of expensive equipment. With the new resin there is also less likelihood of drug interference with test results, and significantly fewer false-positive results occur.

In view of the desirability of a simplified tubeless gastric analysis, a study of the efficacy of the azure A compound was undertaken in comparison with the quinine–resin. Published reports[2-12] have shown that the quinine material differentiated gastric acidity from anacidity, as determined by intubation, in 98 per cent of the 1280 cases.

From the Medical Service, Veterans Administration Hospital, St. Louis, Mo.

The azure A ion exchange compound used in this study was supplied as Diagnex. Improved by E. R. Squibb & Sons, New York, N. Y.

* Field Investigator, National Cancer Institute, U. S. Public Health Service.

## METHOD

Consecutive admissions to a general medical ward of the St. Louis Veterans Administration Hospital were subjected to separate tubeless gastric analysis, using the azure A–cation-exchange compound and the quininium material, Diagnex. The two resin tests were done on consecutive days. This offered proximity of the two tests to minimize the recognized periodic variation in gastric secretory function. Tests were repeated after a 1-week interval to resolve conflicting results with the two resins, as well as in those instances of indeterminate results. Most patients with achlorhydric results on both resin tests were intubated. Ward nurses supervised the administration of the testing material and collection of urine specimens. Most cooperative patients followed printed instructions after an explanation of the test by the nurse.

As with the tube technic, a gastric secretory stimulant was given prior to the resin testing material. Caffeine sodium benzoate is inexpensive and is the most convenient oral secretory stimulus to use with this test. Ethyl alcohol may not be used for this purpose, since this substance is capable of eluting azure A from the resin.[16] Parenteral histamine may be used in re-evaluating results suggestive of achlorhydria with the caffeine stimulant.

### Procedure

The azure A tubeless procedure is as follows:

On the morning of the examination, after fasting since midnight, the patient urinates and discards the specimen. He then takes 500 mg. of caffeine sodium benzoate with one half glass of water. One hour later he urinates in a bottle labeled "Control." He then takes a 2-Gm. dose of azure A–resin (53 mg. azure A/Gm. carboxylic acid compound)[15] in one fourth glass of water. These granules are suspended by agitation, as they do not dissolve. The glass is again filled one fourth full of water and agitated to rinse out any remaining granules; this suspension is swallowed. Two hours after taking the azure A–resin, the patient urinates into l bottle labeled "Assay," being sure to save the entire quantity. He is instructed to empty the bladder completely each time. If he is unable to void on schedule, the test must be abandoned. Catheterization of the bladder is not recommended; this procedure is less desirable than gastric intubation without offering any of the additional advantages of the latter procedure. If the patient wishes to urinate before 2 hours, he may do so but must save as a combined assay specimen all urine voided within this period of time.

The control and assay urine specimens are sent to the laboratory for examination. Visual color comparison is made in a 6-tube comparitor block with ground-glass backing, using natural light. Standards are prepared in test tubes, the minimum required being ones with azure A concentration of 0.3 mg./300 cc. (0.0001% concentration) and 0.6 mg./300 cc. (0.0002%). After diluting the assay urine specimen to 300 cc., an aliquot in a test tube is placed in the front middle hole of the comparitor. The standards are placed in the two lateral holes of the front row. Aliquots of the diluted control urine are placed in test tubes in the holes behind the standards. Proper dilution of the control is that which duplicates the specific gravity of the previously diluted 300-cc. assay specimen. A tube of distilled water is placed behind the assay aliquot. Test tube positions in the comparitor are shown in Fig. 1.

The color of the assay tube is compared with the standards by holding the comparitor block before a source of natural light. If color intensity exceeds the 0.6 mg. standard, free hydrochloric acid is present. Otherwise, the assay and control aliquots should be acidified to *p*H 1–2 with concentrated hydrochloric acid and boiled in a water bath for 10 minutes to release the dye which may exist in a colorless conjugated form. The test tubes are removed from the water bath and allowed to cool to room temperature. Color development may require as long as 1 hour. The boiling process may cause previous color to disappear, but it will reappear on cooling.

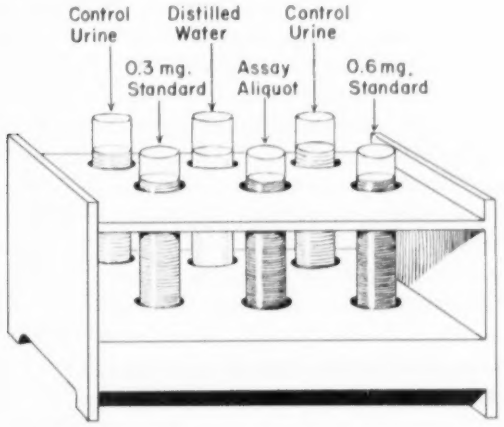


***Fig. 1.*** **Front view of visual color comparitor block demonstrating arrangement of the test tubes for the azure A urine determination in the tubeless gastric analysis.**

TABLE 1. Interpretation of Azure A– and Quinine-Resin Results

| Interpretation | Azure A–Resin (mg./300 cc. urine) | Quinine–Resin ($\mu$g./300 cc. urine) |
|---|---|---|
| Positive (Free HCl) | >0.6 | >25 |
| Indeterminate | 0.3–0.6 | 15–25 |
| Negative (No free HCl) | <0.3 | <15 |

A color intensity remaining less than 0.3 mg. indicates the absence of free hydrochloric acid. Readings between 0.3 and 0.6 mg. are indeterminate, and the test should be repeated after a lapse of 7 days. Patients should be cautioned that a blue coloration of urine persisting a few days following the test is no cause for alarm.

The laboratory technic for the quininium resin has been described previously[10] and will not be outlined here. In this study, when intubation gastric analysis was performed, histamine was administered (0.1 mg./10 kg. body weight) to insure sufficient gastric secretory stimulation.

Table 1 outlines the laboratory values for the various interpretations of tests with the quinine– and azure A–resins.

## RESULTS

During this study, sufficient data for interpretation were obtained in 93 patients, of which 92 were males. In some of the patients one or more resin tests were repeated to clarify original results; therefore, there were 103 tests with the azure A material and 106 with the quinine–resin. In a severely jaundiced patient, the results on one test with each resin are excluded from the final tabulation because excessive bile in the urine prevented interpretation. In evaluating the results, arbitrary categories of "Excellent," "Good," and "Poor" have been adopted. These classifications are defined in Table 2, which illustrates the various combinations of results for each classification and summarizes findings in the study.

Excellent or good agreement of azure A– and quinine–resin results occurred in 89.2 per cent of initial tests. Repeated examination of selected patients in the Good and Poor categories increased the combined results of the Excellent and Good classifications to 95.7 per cent.

The multiple test procedures reduced the poor results from 10.8 per cent to 4.3 per cent. Three of the 4 patients remaining in the Poor classification did not have repeated resin tests. Table 3 outlines data on patients with poor results.

**TABLE 2. Comparison of Agreement of Results After One Test with Each Resin and After Repeating Tests in Selected Cases**

| Classification | Test combination | | 1 Test | | | Repeated tests | | |
|---|---|---|---|---|---|---|---|---|
| | Azure A–resin | Quinine–resin | No. patients | | % | No. patients | | % |
| Excellent | Positive | Positive | 56 | 71 | 76.3 | 63 | 78 | 83.9 |
| | Negative | Negative | 15 | | | 15 | | |
| Good | Positive | Indeterminate | 4 | 12 | 12.9 | 6 | 11 | 11.8 |
| | Negative | Indeterminate | 4 | | | 3 | | |
| | Indeterm. | Positive | 2 | | | 0 | | |
| | Indeterm. | Negative | 2 | | | 2 | | |
| Poor | Positive | Negative | 5 | 10 | 10.8 | 3 | 4 | 4.3 |
| | Negative | Positive | 5 | | | 1 | | |
| TOTAL | | | | 93 | 100% | | 93 | 100% |

**TABLE 3. Summary of Patients with Poor Correlation of Results with Azure A– and Quinine Resin**

| Patient (age, race, sex) | Diagnosis | Test results | | Comment |
|---|---|---|---|---|
| | | Azure A | Quinine | |
| O.R.C. (67-W/M) | Severe rheumatoid arthritis | Positive | Negative | |
| W.A.D. (65-N/M) | Arteriosclerotic heart disease | Positive | Negative (x2) | Upper GI series; (?) Active duodenal ulcer |
| R.J.K. (38-W/M) | Mucous colitis | Negative | Positive | Upper GI series; negative |
| R.S. (59-N/M) | Multiple myeloma | Positive | Negative | |

In 15 patients there were achlorhydric results with both resins. Five of these apparently were given inadequate gastric secretory stimulation. During the early phase of the study, 250 mg. of caffeine sodium benzoate was administered rather than the more accepted 500 mg. dosage. Although subsequent intubation gastric analysis revealed absent or low fasting-free-acid values in these subjects, histamine stimulation yielded free acid. The remaining 10 patients received the larger dosage of caffeine drug. Seven of these patients were intubated, and achlorhydria persisting after histamine administration was noted in 6. The seventh had no fasting free hydrochloric acid and a hypochlorhydric response to histamine. Table 4 is a summary of the patients with achlorhydric results with both azure A– and quinine–resins, after receiving 500 mg. of the caffeine secretory stimulant.

**TABLE 4. Summary of Patients with Achlorhydria Results with both Azure A-and Quinine-Resin**

| Patient (age, race, sex) | Diagnosis | Tube results (Degree of Free HCl) | | Gastroscopy findings | Upper GI Series | Comment |
|---|---|---|---|---|---|---|
| | | Fasting | Post-histamine | | | |
| 1. 60-N/M | Arteriosclerotic heart disease | 0 | 0 | Superficial gastritis | Negative | .. |
| 2. 39-W/M | Arteriosclerotic heart disease | 0 | 8 | .. | .. | .. |
| 3. 60-N/M | Rheumatic heart disease | 0 | 0 | (a) Gastric atrophy, ? infiltrative disease; (b) superficial gastritis | Neg. | Gastric biopsy: chronic gastritis |
| 4. 29-W/M | Laennec's cirrhosis | (Left hospital prior to intubation) | | | Neg. | .. |
| 5. 65-W/M | Hypertensive cardiovascular disease | (Left hospital prior to intubation) | | | Neg. | Severe renal insufficiency and azotemia |
| 6. 60-W/M | Asthma | 0 | 0 | .. | .. | .. |
| 7. 30-W/M | Regional enteritis | 0 | 0 | .. | Neg. | .. |
| 8. 65-W/M | Acute myocardial infarction | 0 | 0 | .. | Neg. | .. |
| 9. 66-W/M | Acute gastrointestinal bleeding, unknown origin | 0 | 0 | Procedure unsatisfactory | Neg. (Except evidence of subtotal gastrectomy) | Had subtotal gastric resection for bleeding d.u. 1948 |
| 10. 57-N/M | Hypertensive cardiovascular disease | (Left hospital against medical advice before intubation) | | | | .. |

## DISCUSSION

Since periodic variation in gastric secretory function occurs, the results which are classified as "good" do not reflect upon the accuracy of one test compared with the other. Therefore, it is felt that the combined Excellent and Good categories represent satisfactory agreement of results. On a single-test comparison there was 89.2 per cent agreement; this increased to 95.7 per cent with repeated-test comparison. It has been shown that the quinine-resin reproduces intubation results in 98 per cent of tests.[2-12] The findings of this study indicate that the new dye–resin approximates this degree of accuracy. Since false-positive results are infrequent with tubeless gastric analysis, a single azure A–resin test result indicative of free acid is highly reliable. In addition, an achlorhydric result confirmed by more than one test with the dye–resin is reliable evidence of an inability to secrete acid. Although a single negative test frequently indicates persistent achlorhydria, it may also occur with physiological secretory variation and, temporarily, with various disease states, or with inadequate gastric secretory stimulus.

### Time Required

In this investigation, there was no expectation that the new azure A–resin would be shown to be a more accurate testing material than the quinine compound. The greater simplicity of laboratory procedures with the new material was the main stimulus for this study, since it would be better suited to mass screening for achlorhydria if as reliable as the quinine–resin. One advantage claimed for the tubeless gastric analysis is the small amount of technician's time required to perform the laboratory procedures. The quinine test takes about 8 minutes to perform, according to Harkness and Durant.[7] In our observations of the azure A procedure, about 1½ minutes was required for each test when direct observation was possible. When boiling was required to develop the color, up to 1 hour of waiting for color development was necessary. However, less than 4 minutes for each test was required by the actual work of the laboratory method. In this study, boiling was necessary in one half of the tests in order to develop sufficient color for a positive result. An additional one fourth of the specimens were boiled, but color intensity remained within the negative or indeterminate range. In virtually all aliquots color developed by 1 hour; interpretation at this interval after boiling seems reliable.

### Color Comparison

Although various shades of color may appear with or after boiling, there is usually no problem in comparison with the standards. If control specimens are diluted to the same specific gravity as the 300-cc. assay specimen (not to the same volume) and otherwise handled in the same manner as the test urine (acidified and boiled if required), this modifies the color of the standards to a comparable hue for satisfactory determination of relative color intensity. The necessity of acidifying urines prior to boiling has not been established, although our data show that occasionally more color appears in acidified specimens. Further simplification of methods for color development is receiving study.

### Hydrogen-Ion Exchange

In performing tests with the two resins, simultaneous administration of the quinine and azure A materials is not advisable. Our experience with this combined procedure demonstrated that quinine exchange for hydrogen ions is preferentially carried out. Only with a high degree of acidity was the azure A also dislodged from its resin. The in vitro studies of Segal[15] demonstrated this preferential quinine release.

### Conclusions

Although some slight modification of laboratory procedures for the azure A–resin may be developed, the present methods are more rapid and less complicated than those for the quininium compound. The test may be readily and reliably done in a hospital laboratory or physician's office by a technician after a brief period of experience with the technic and interpretations. Its principal potential usefulness is as a screening procedure for achlorhydria when a qualitative result is all that is required.

## SUMMARY

A new dye–resin compound for the tubeless gastric analysis has been shown to reproduce the results obtained with the quinine compound, Diagnex, in approximately 96 per cent of patients tested with both substances. The technic with this azure A–resin is simpler than with the quinine substance and has a comparable accuracy. Numerous technical factors in the azure A–resin procedure have been discussed.

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# *Amebiasis: A Review*

## I. Pathogenesis, Pathology, and Clinical Manifestations

HARRY SENECA, M.D.

### PATHOGENESIS

Amebic infection of the host takes place through the ingestion of encysted organism. Trophozoites are readily destroyed in the gastric secretions, but the cysts pass unchanged in the stomach and the small intestine. Excystment takes place in the distal part of ileum and cecum. The cyst wall becomes permeable through the action of the intestinal secretions, thus activating the four nucleated cyst into four motile metacysts or metacystic trophozoites.

The invasion of the colonic wall is due to the action of the cytolytic enzymes secreted by the trophozoites, motility of the amebas, and the normal intestinal bacteria which produce cytolytic enzymes, lower the tissue resistance, and produce secondary bacterial infection and inflammation. The trophozoites multiply by binary fission in the tissues, and pass into the lumen of the bowel where encystment takes place, otherwise they will perish. Encystment never takes place in the tissues. No excystment of these cysts occurs in the same host, unless they are swallowed and reach the colon via the stomach.

The number of cysts voided per day varies from 330,000 to 45 million, with an average of 14.52 million, and occurs in cycles or crops. In the rhesus monkey, on high-carbohydrate diet, the maximum number of cysts occurs every 7 days, and the elimination cycles range from 4 to 14 days. Apparently there is no difference in the virulence of the small and large races of ameba, and there is evidence that the small race may transform into the large variety. All strains, including the cysts from asymptomatic cyst carriers are pathogenic, but there may be a difference or variation in the virulence.

There may be a natural immunity or host resistance, but more probably this is due to lack of exposure. Some individuals may possess a relative immunity, but all persons including the cyst carriers should be carefully studied and watched for minor and vague symptoms. As

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soon as the equilibrium between the host and the parasite is upset, clinical amebiasis may follow. Complement-fixation test is positive in hepatic and intestinal amebiasis, but the antibodies are lost when the patient is completely cured or the amebas are destroyed. Recovery from amebiasis does not confer protection against reinfection. Immunity in amebiasis is partial, transient, and has no preventive application.

Although clinical amebiasis is not known to occur among animals, monkeys, dogs, pigs, and rats have been found naturally infected. These animals as well as kittens, guinea pigs, rabbits, and mice can be experimentally infected.

## METHOD OF TRANSMISSION and INCIDENCE

The method of transmission is through contamination of the food and drinks with the cysts by food handlers, flies, and the use of the human excreta as fertilizers. Neglect of hygienic measures in prisons, camps, schools, orphanages, and particularly in mental hospitals may cause serious epidemics. Children below 5 are rarely infected, and the highest rate of incidence is among persons 26 to 30 years of age. Males are more frequently infected, and in hepatic amebiasis the ratio is 16.4 males to 1 female. All races are susceptible to infection (Figs. 1 and 2), but the white race in tropical climates suffers very acutely, while the natives are resistant. It is more prevalent in the poor and less-educated class than in the higher economic group.

### Survival of Amebas

In rectosigmoidal amebiasis the bowel movements are frequent, stools are semifluid or fluid, and trophozoites are passed in the stools. In cecal amebiasis the movements are slowed down, stools are constipated, and cysts are passed in the stools. The trophozoites are short-lived, while the cysts are resistant and survive about 12 days in the stools and up to 30 days in water. Drying and heat at 50°C. is lethal.

Water for drinking purposes should be hyperchlorinated. Cationic detergents are cysticidal in 30 ppm in 10 minutes and in 10 ppm in 2 hours. Ozone is highly cysticidal and its action is not influenced by *p*H, organic nitrogen, or temperature. The cysts and trophozoites survive in the vomitus of the fly 17 minutes. The cysts are viable in the vomitus 64 minutes, and in the stools 254 minutes. In cockroaches the cysts survive 48 hours.

*Fig. 1.* Global epidemiology of amebiasis. (Compiled from Simmons *et al.*[14])

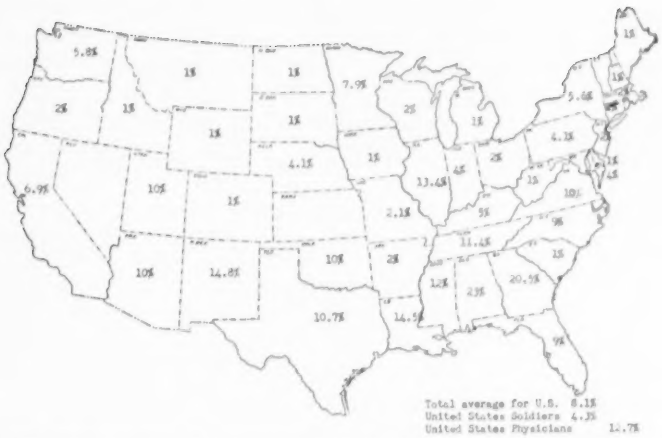


*Fig. 2.* **Incidence of amebiasis in the United States. (Compiled from Faust *et al.*,[7] Anderson *et al.*,[1] and others)**

## PATHOLOGIC FEATURES

### Process of Invasion

The metacystic trophozoites invade the mucosa of the ileocecal region where the primary lesions are most frequently located. Secondary lesions appear distal to the cecal segment. The cytolytic enzymes, the motility of the ameba, and secondary bacterial associates help establish the beachhead which is either at the tip of the interglandular prominence, part way down the crypt, or at the base of the crypt. The colonization spreads rapidly in the less dense submucosa and is usually limited by the somewhat resistant muscularis mucosae. The resulting lesions have pinpoint site of penetration and undermined tunnels with bullous bases, while the intervening areas are undamaged.

Secondary colonization occurs in the distal portions of the colon. The intervening mucous membrane at first looks normal, but as the pathology becomes extensive the roof of the tunnel collapses, exposing ulcers which have dirty necrotic gelatinous material in the base, containing dead cells and trophozoites. The edges of the ulcer are heaped up, ragged, and overhanging. The ulcers vary in size, and may be round, oval, or irregular due to coalescing of smaller ulcers. Buttonhole ulcers may result when a sinus communicates between two ulcers beneath normal mucous membrane. The ulcers may extend through the submucosa and muscularis and rarely perforate. Thrombotic lesions in the portal vein may follow due to the invasion or erosion of the

amebas into the mesenteric veins, giving rise to hepatic amebiasis. If they erode into the mesenteric lymphatics, the amebas reach the lungs via the heart, and in case they enter the systemic circulation, they may give rise to lesions in the brain, spleen, kidneys, etc. The incidence of hepatic amebiasis in a series of 2878 cases was 3.48 per cent and in a second series of 7424 cases was 28 per cent.

### Site of Lesions

The amebic lesions in the colon (Fig. 3) occur mainly in places where there is fecal stagnation. The commonest site is the cecum, and next is the rectosigmoid segment. Diffuse or generalized lesions also occur along the entire length of the colon, or they may be restricted to the ascending, transverse, and descending segments, hepatic and splenic flexures, and the distal portion of ileum.

### Microscopic Appearance of Tissues

Microscopically there is a scarcity of granulocytes and the tissue reaction to the invading pathogen is poor. Lymphocytes, plasma cells, and macrophages prevail, and there is proliferation of fibrocytes and capillary endothelium. Secondary polymorphonuclear infiltration is

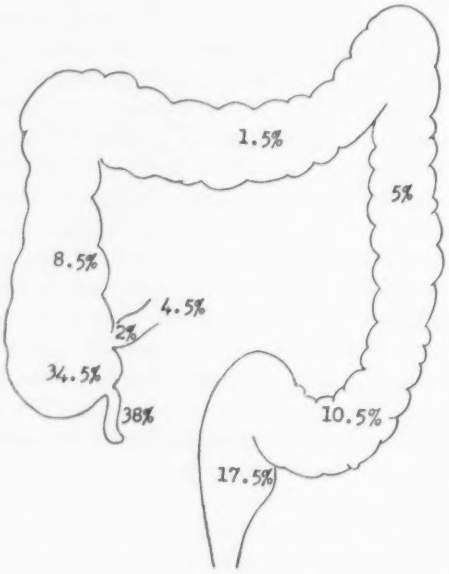


*Fig. 3.* **Distribution of amebic lesions in the colon (from Clark).**

| | |
|---|---|
| General colonic involvement | 56.5% |
| Liver involvement | 44.5% |
| Lung | 4.0% |
| Brain | 1.0% |
| Portal thrombosis | 0.5% |
| Renal vein thrombosis | 0.5% |
| Inferior vena cava | 0.5% |
| Total cases | 198 |

due to the associated bacterial invasion. Necrosis and abscess formation are usual manifestations. The bacterial infection is usually moderate, unless the virulence of the intestinal flora has been enhanced or altered. The local tissue defenses repair the injury and prevent extensive pathology, perforation, and severe hemorrhage. Occasionally amebomas are formed due to an exuberant connective tissue response to the inflammatory process, similar to keloid formation. This granulation tissue mass shows signs of chronic inflammation in the form of lymphocytes, plasma cells, macrophages, eosinophiles, an occasional ameba, and a minimum of tissue destruction. When the inflammatory reaction subsides the lymphocytes disappear and there is very little cicatrization or scar tissue formation, but in severe ulcerative lesions there may be marked fibrosis leading to rigid, thick, and stenotic colon. In the asymptomatic carrier tissue destruction and fibroblastic response are reversible, leaving no trace of pathology.

**Hepatic Involvement**

No hepatotropic strains of ameba have been reported. The hepatic lesions are due to the fact that the portal system which drains the intestinal tract ends in the liver. The majority of amebas do not survive in the liver, provided this organ is normal, and has not been injured by alcohol, malaria, syphilis, malnutrition, or concomitant secondary bacterial associates arriving with amebas. In the presuppurative stage (hepatitis), there is fatty infiltration and degeneration of the liver cells manifested by pyknosis, karyolysis, and then complete destruction. This is associated with a low-grade inflammation characterized by the infiltration of lymphocytes, macrophage cells, fibroblasts, and occasional polymorphonuclear leukocytes. If there is superimposed bacterial infection, the polymorphonuclear infiltration is very marked and a purulent reaction will follow. As the inflammation becomes chronic, the connective tissue increases, the capsule is thickened, connective tissue strands are destroyed, there is peripheral fibrosis, and ultimately an abscess cavity is formed. Amebas are numerous in the viable tissues in the wall of the cavity, in the small and early abscesses, but tend to decrease in number as the pathology becomes chronic. The contents of the abscess are chocolate colored and no cellular detail can be identified. In a series of 424 cases, 55.2 per cent had amebas in the pus. The pus was sterile in 83.9 per cent of 386 cases. In another series of 46 patients, 17.4 per cent had amebas in the pus and 36.1 per cent in the stools. Among 1075 cases, 59 per cent had solitary abscesses and 41 per cent had multiple abscesses. The

abscess is usually located in the right lobe and may vary in size from 1 to 20 cm. in diameter. An amebic abscess may heal spontaneously (rare) or rupture either into the peritoneal cavity or neighboring viscera, through the diaphragm into the pleural cavity and give rise to empyema, or into the lung and be expectorated through the bronchus.

### Rare Types of Amebiasis

Pulmonary amebiasis is secondary to hepatic amebiasis, or it may be primary and hematogenous. Amebiasis cutis may be the result of direct extension into the skin via sinuses or fistulas. Amebiasis of the genitourinary tract may be due to the extension of the disease from the anogenital orifice. Amebic abscess of the brain, spleen, kidney, and meninges is hematogenous in origin.

## CLINICAL MANIFESTATIONS

### Acute Amebic Dysentery

Acute amebic dysentery or colitis may be mild, moderate, or fulminating (gangrenous). The incubation period may vary from a week to many months. In the case of the asymptomatic carrier it may be years. The onset may be sudden or may follow repeated attacks of diarrhea or enteritis. The patient has severe pain in the abdomen and an intense desire to defecate. At first the stools are partly formed and contain mucus, but soon they become fluid and the amount of mucus increases and blood appears. Shreds of mucus membrane may be passed, and the entire stools consist of blood and mucus. The number of movements may vary from 15 to 35 or more. Tenesmus may become very marked. There may be nausea and vomiting, and rapid dehydration may result in the loss of fluids and electrolytes. The acute abdominal pains or cramps may be associated with chilly sensations, but usually there is no fever. In severe cases, pyrexia and leukocytosis are common, but in mild and moderate cases the intestinal symptoms prevail.

### Chronic Amebiasis

#### *Asymptomatic Complaints*

The asymptomatic or cyst-carrier state is a condition in which there is a well-balanced equilibrium between the host and the parasite. These patients have minor gastrointestinal complaints in the form of indigestion, particularly after fatty meals, anorexia, eructations, flatulence, coated tongue, halitosis, irregular bowel movements, diarrhea,

constipation or alternating attacks of diarrhea and constipation, tenderness over the cecum or sigmoid, thickening of the colon, hepatomegaly, nervous irritability, and so on. Eventually resistance is lowered, and clinical amebiasis will develop.

***Symptoms Resembling Other Conditions***

Symptomatic amebiasis is often disguised in the form of another condition or syndrome and has protean manifestations.

**Peptic Ulcer.** It may be mistaken for peptic ulcer clinically, but the internist will realize that the symptoms of the patient are not typical ulcer symptoms, and the gastrointestinal x-ray does not reveal the presence of an ulcer. Hunger pains are usually absent. If present, they may not be relieved by food. There may be heaviness and bloating after meals. The epigastric discomfort is poorly localized and the patient is very vague in the description of his pain. The pain does not awaken him from his sleep, and does not radiate. Alcohol, fatty diet, fried food, and spices aggravate the dyspeptic symptoms. There is a certain degree of irritability and nervousness which may lead to the diagnosis of nervous stomach or gastric neurosis.

**Gallbladder Disease.** In a certain number of cases, the symptoms resemble that of chronic cholecystitis and/or cholelithiasis. The dyspeptic symptoms are common when the diet is rich in fats or the patient ingests fried food. There may be vague pain in the right upper quadrant or in the epigastrium, but gallbladder is not tender. Flat films and cholecystograms do not reveal any pathology in the biliary passages.

**Appendicitis.** In amebiasis primarily involving the cecum, there may be recurrent attacks of sharp abdominal pain localizing in the right lower quadrant as in acute appendicitis. At other times the mild pain localized in this area is often diagnosed as chronic appendicitis. Localized rigidity may be absent, and repeated white blood cell count and differential count will eliminate the latter diagnosis. The presence of *E. histolytica* in the stools is not conclusive, because a cyst carrier may have surgical appendicitis. Operations are contraindicated in intestinal amebiasis; therefore amebic appendicitis should be clearly distinguished from surgical appendicitis. Sections of the appendix will reveal the presence of amebas in the wall. Amebic appendicitis is both a clinical and pathologic entity, and is associated with colonic amebiasis.

**Psychoneurosis.** Psychoneurosis may be a manifestation of chronic

amebiasis. In chronic infection there is a mild toxemia. The patient may be aware of slight discomfort and may have a readily overlooked neurasthenia. Some patients may show indefinite disturbances such as vague subjective symptoms of loss of weight, energy, and appetite; mental and physical lassitude; vasomotor and nervous disturbances; myalgia; arthralgia; lack of interest in work; and diminished power of concentration at work. There may be associated minor gastrointestinal disturbances. Before making a clinical diagnosis of psychoneurosis and referring the patient to the psychiatrist, the general practitioner, internist, or gastroenterologist should rule out the possibility of chronic amebiasis.

**Hepatic Amebiasis**

A number of clinicians and investigators in this field have speculated as to the nature of a condition which is frequently referred to as amebic hepatitis. Others prefer to call it the presuppurative stage of amebic abscess because the pathologic studies of the sections of the liver in human amebic hepatitis and in the experimental hepatic complication in the laboratory animals do not reveal a clear-cut distinction between the presuppurative (hepatitis) and abscess stages. It is a continuous process. Most of the amebas which reach the liver are destroyed; those that survive give rise to tissue destruction and the formation of minute abscesses which eventually coalesce to form an amebic abscess. Liver biopsy shows evidence of subacute hepatitis, focal in distribution and most marked in the periportal areas. Microscopically there is infiltration of lymphocytes and plasma cells, and rarely polymorphonuclears. There is an increase in fibrous tissue around the biliary triad with a tendency to regeneration of the parenchymal cells. No amebas are found. In this clinical entity, one often observes an enlarged liver, tenderness in the right upper quandrant, digestive disturbances, abnormal hepatic function by laboratory tests, and at times an accompanying intestinal amebiasis.

Amebic hepatitis should not be confused with viral or nutritional liver diseases which may occur in patients having intestinal amebiasis. It may follow within a few weeks or months and even years following the invasion of the intestinal wall. It is more common in the warmer climates, and among newcomers in endemic areas. In Panama, 50 per cent of patients with intestinal amebiasis may have hepatic involvement. In the southern United States, 5 per cent of 745 cases of intestinal amebiasis developed hepatic complications, and in a mental

hospital in California, among 371 cases of intestinal amebiasis, 29 were diagnosed clinically as amebic hepatitis, but only 9 out of 11 biopsies of the liver showed evidence of hepatic amebiasis (Radke 1954; Weiser *et al.*, 1953; Brooks *et al.*, 1953; Nelson *et al.*, 1955).

Amebic or solitary abscess of the liver usually has a sudden onset, and is characterized by chills, fever, perspiration, pain, and tenderness in the right upper quadrant, referred to the back or right shoulder. The patient is acutely ill, toxic, and has general malaise and debility. There is marked hepatomegaly with rounded edges (no liver edge is palpated). The gastrointestinal symptoms include nausea, vomiting, anorexia, rarely jaundice, constipation, diarrhea, blood and mucus in the stools, tenesmus, hemorrhoids, etc. Laboratory examination reveals a marked leukocytosis with an increase in the number of young granulocytes. *Endameba histolytica* may be found in the stools in a third of the patients, and in pus aspirated from the liver in a sixth. The profile of liver tests may be normal, but there may be a delay in the excretion of bromsulfalein and rarely a positive cephalin-flocculation test. X-ray examination shows an elevation, tenting and fixation of the right half of the diaphragm, congestion of the base of the right lung, and some effusion in the right pleural cavity. The aspiration of chocolate-colored pus confirms the diagnosis of amebic abscess of the liver.

**Ameboma**

Ameboma or amebic granuloma of the intestine is a localized thickening of the intestinal wall about an ulceration, with narrowing of the lumen, and the presence of a palpable mass which can be mistaken for a neoplasm. The most frequent locations are the rectum, cecum, transverse colon, sigmoid, and ascending colon, and at times multiple sites. The pathology is ulceration, thickening of the wall, minute miliary abscesses protruding into the lumen, the surrounding mucosa overlying the summit of the lesion. At times the mucosa reestablishes itself over the defect, leaving the lesion confined to the submucosa. The mucosa may slough due to the undermining of the lesions. Microscopically eosinophilic infiltration is very common, although there may be lymphocytes, polymorphonuclears, plasma cells, histiocytes, foreign-body giant cells, and *Endameba histolytica*. There is accompanying edema, hyalin deposits, and fibroblastic proliferation. The clinical picture includes diarrhea, lower abdominal cramps, loss of weight, fever, rectal mass, abdominal tenderness, hepatomegaly, in-

testinal obstruction syndrome, amebiasis cutis, leukocytosis, filling defects by barium enema x-ray examination, presence of *E. histolytica*, abdominal or rectal mass by sigmoidoscopic examination, and the disappearance of the lesion following the antiamebic treatment. In 30 per cent of the cases, the diagnosis is made at post mortem. The mortality rate is 40 per cent due to faulty diagnosis and surgical intervention for intestinal obstruction or neoplasm.

*(To be continued; References will appear at the end of Part II.)*

# CASE REPORT

# Carcinoma of the Pancreas

## Some Unusual Manifestations

G. A. GRESHAM

THE CLINICAL DIAGNOSIS of carcinoma of the pancreas is often difficult and although important additions have been made by various authors[2, 5, 11, 13, 14] to the early account of the clinical features by Bard and Pie,[1] there are many cases in which carcinomatosis is the only possible clinical diagnosis and no primary neoplasm is found during life. It is perhaps less widely appreciated that early metastatic deposits may present as primary tumors in other organs. The purpose of this paper is to report cases with unusual and misleading clinical and pathologic features. In two of these cases the histologic examination of biopsy material and the macroscopic postmortem findings were both compatible with the incorrect clinical diagnosis. The diagnosis of carcinoma of the pancreas was made only after microscopic examination, and was based on the following criteria:

- The presence at the edges of the tumor of histologic gradations between normal pancreas and tumor tissue.
- Permeation of veins and perineural lymphatics in and around the gland by tumor cells.
- The presence of the maximum deposits in those lymph nodes draining the pancreas, more distant lymph nodes being correspondingly less affected.

### CASE 1

**Columnar-celled Carcinoma of the Head of the Pancreas Presenting as Carcinoma of the Bronchus**

T. C., a 69-year-old male, was admitted to the hospital in September, 1954, with acute retention of urine. Prostatectomy was performed. Left-

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I am grateful to Dr. A. M. Barrett for his help and advice in the preparation of this paper; to Dr. L. Cole, Dr. A. P. Dick, Mr. McN. Truscott, and Mr. O. Lloyd for permission to make use of the clinical notes of these cases. Mr. S. Patman and Miss S. Westoby prepared the photographs.

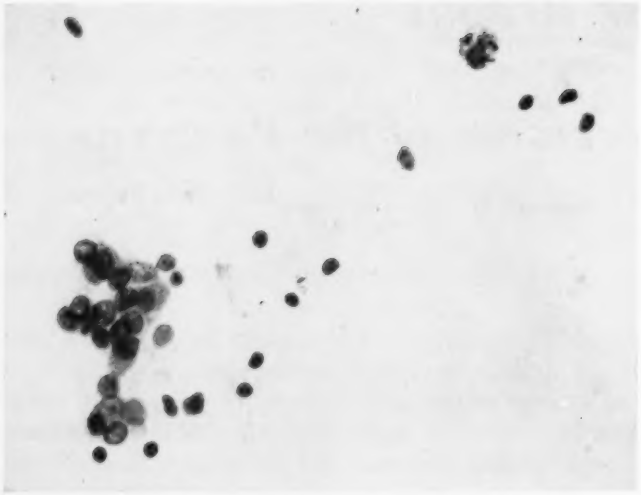

*Fig. 1.* **Bronchial aspirate containing a clump of neoplastic cells.** (× 580).

sided pleuritic pain had been present for about 4 weeks before admission. Examination disclosed a left pleural effusion. Cytologic examination of the sputum and pleural fluid showed no tumor cells. Bronchoscopy did not reveal any lesion. A bronchial aspirate contained clumps of tumor cells (Fig. 1).

The patient was readmitted in January, 1955, with abdominal pain due to purulent cystitis. Bilateral basal consolidation and pleural effusions were diagnosed clinically and radiologically. Obstructive jaundice developed about two weeks before death and the liver became palpable. He became progressively more jaundiced and cachectic and died on January 31, 1955, 6 months after the onset of his chest pain. The clinical diagnosis before death was bronchial carcinoma.

### *Postmortem Findings*

Necropsy 48 hours after death showed an ill-defined nodule (approx. 1.5 cm. diam.) in the head of the pancreas, adjacent to the termination of the common bile duct. The main pancreatic duct was dilated, and the body and tail of the organ, although firm, were not grossly abnormal. Several enlarged lymph nodes along the upper border of the gland and around the celiac axis contained secondary carcinoma. The liver was moderately enlarged and the portal tracts were macroscopically thickened by strands of tough white tumor tissue. There was no ascites, and no metastases were present on the peritoneal surfaces. The right pleural cavity contained 500 cc. and the left 150 cc. of yellow fluid. Numerous small

metastases were scattered throughout both lungs mainly in the subpleural zones. In the lower lobes there was consolidation and collapse, with scarring and puckering of the pleural surface. In these lobes the bronchi and pulmonary vessels were surrounded by tough white tumor tissue. Mucosal roughening by growth was found only in one of the left lower-lobe bronchi. The hilar and mediastinal lymph nodes were normal in size and appearance. No secondary deposits were found in any other organs.

### *Histology*

The nodule in the head of the pancreas was found to be a mucin-producing columnar-celled carcinoma. Other sections from the head of the gland showed considerable atrophy of the parenchyma with increase in fibrous tissue and infiltration by carcinoma cells. Secondary deposits were present in pancreatic lymph nodes and in the portal tracts of the liver. Diffuse lymphatic permeation was present throughout both lungs, with the formation of "acini" of columnar carcinoma cells within the alveoli in many areas. The walls of some bronchi in the left lower lobe were infiltrated. Recent and organized antemortem thrombi occluded many branches of the pulmonary artery.

## CASE 2

### Columnar-celled Carcinoma of Head of Pancreas Presenting as Carcinoma of Bronchus

H. H., a 57-year-old male, was admitted to the hospital in August, 1950. He had suffered from a winter cough for many years, but following an attack of "influenza" 9 months before had become progressively more breathless.

On examination he was obese; the abdomen was distended and there was tenderness in the right hypochondrium; but no masses could be felt. There was impairment of percussion note and reduced air entry in all lung zones and numerous coarse rales at both lung bases. The left supraclavicular lymph nodes were enlarged. Radiography of the chest showed no definite abnormality. The provisional clinical diagnosis was carcinoma of the bronchus, chronic bronchitis, and emphysema. A lymph node biopsy was planned but the patient died suddenly 10 days after admission.

### *Postmortem Findings*

Necropsy 24 hours after death showed the head of the pancreas to have been replaced by a tumor (about $8 \times 4 \times 4$ cm.), in the substance of which there were two cystic spaces (the larger 4 cm. diam.) containing yellowish brown fluid. The common bile duct was patent. Secondary carcinoma was present in the lymph nodes along the upper border of the pancreas, around the celiac axis, and in the left supraclavicular and deep cervical regions.

The lungs were permeated by secondary carcinoma, and a tumor deposit was present in the medulla of the right suprarenal gland. No carcinoma was found in the liver. There were no metastases on the peritoneal surfaces or in any other organ.

### *Histology*

The tumor in the head of the pancreas was an acinar and papillary columnar-cell carcinoma producing a little mucin. Neoplastic cells were infiltrating the sclerosed and atrophic glandular parenchyma. In other parts of the gland there was slight chronic inflammatory cellular infiltration of the interstitial tissue, and many small veins contained antemortem thrombus. Secondary carcinoma was present in lymph nodes and the suprarenal medulla. The lungs showed lymphatic permeation by secondary carcinoma.

## CASE 3

### Squamous Carcinoma of the Pancreas

M. W., a 39-year-old female, had suffered from lassitude for 3 months, with attacks of epigastric discomfort unrelated to food. She was admitted to hospital on February 17, 1947, because an abdominal mass had been felt.

She was clinically anemic (hemoglobin 6.3 Gm.) and slightly jaundiced. The liver was enlarged and nodular; a barium meal showed no abnormality in the stomach or duodenum. The abdominal mass increased in size, and a laparotomy performed on March 25, 1947, showed a large liver containing many metastases of a carcinoma, the primary site of which was not determined at operation. The patient died 4 days later.

### *Postmortem Findings*

The lower half of the head of the pancreas was entirely replaced by firm neoplastic tissue which was also infiltrating the wall of the duodenum. The common bile duct lay above the growth and was not obstructed. Several large lymph nodes containing growth were found in the portal fissure and along the lesser curvature of the stomach. The liver was considerably enlarged and almost entirely replaced by secondary deposits. Recent antemortem thrombus was found in the superior mesenteric vein. The tracheobronchial and left supraclavicular lymph nodes contained metastases; a few branches of the pulmonary artery to the right lower lobe contained antemortem thrombi.

Nothing abnormal was found in the other organs.

### *Histology*

The growth in the pancreas was a columnar- and squamous-cell carcinoma of the pancreas forming solid islands of cells in a fibrous stroma.

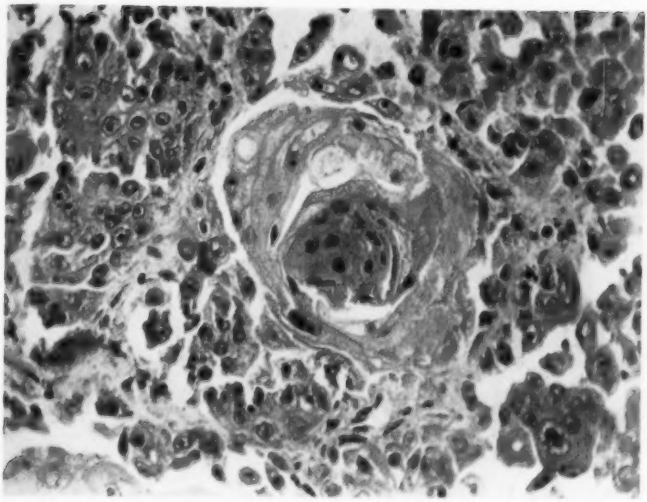

*Fig. 2.* **Cell nest in a deposit of pancreatic carcinoma in a supraclavicular lymph node** (× 320).

Sections taken from the supraclavicular lymph node showed secondary deposits of a keratinizing squamous carcinoma (Fig. 2).

## CASE 4

### Carcinoma of the Pancreas Presenting as Carcinoma of the Uterine Body

R. R., a 66-year-old female, was admitted to the hospital on May 27, 1954, with a history of offensive vaginal discharge of 10 years' duration. Swelling of the abdomen with epigastric pain radiating through to the back together with bleeding per vaginam had been present for the past year.

Examination revealed a large, firm swelling rising out of the pelvis. Hard irregular plaques were detected on the vaginal wall, and the clitoris was enlarged. Sparse hairs were present on the chin. These clinical findings led to the preliminary diagnosis of a virilizing tumor of the ovary. Uterine curettage revealed a well-differentiated tubular columnar-cell carcinoma (Fig. 3). A similar appearance was seen in a biopsy taken from the posterior vaginal wall. A skiagram of the skull showed a normal sella turcica, and the urinary 17-ketosteroid excretion was within normal limits. The blood urea was 115 mg./100 cc. 4 days before death.

#### *Postmortem Findings*

The pancreas was greatly enlarged and entirely replaced by a grey-white mass of growth; the duodenum was not infiltrated. The uterus was diffusely

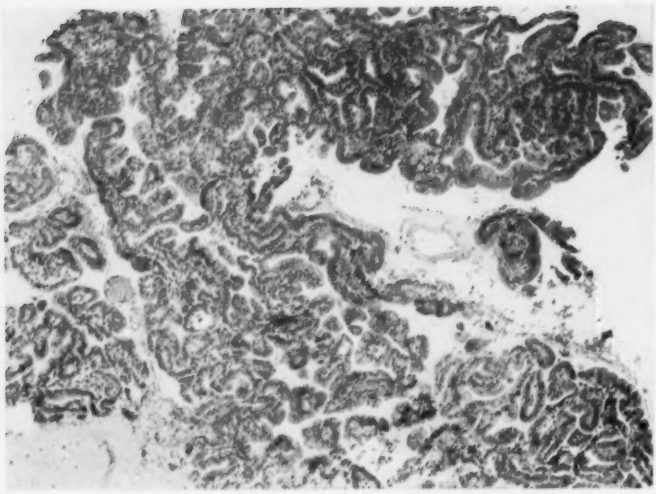

*Fig. 3.* **Products of uterine curettage showing a columnar-cell carcinoma (× 72).**

enlarged by growth, and the small intestine was adherent to its fundus. Nodular masses projecting into the vagina almost completely obliterated its cavity. The cut surface of the body of the clitoris showed grey-white nodules of growth extending into the corpora cavernosa. The ovaries were normal (Fig. 4). There was considerable enlargement of the para-aortic lymph nodes, which were almost entirely replaced by growth, and a nodule of growth was detected in the lower pole of the left lobe of the thyroid. No metastases were found in the lungs but there were recent thrombi in branches of the pulmonary artery to the right lower lobe.

### *Histology*

The growth in the pancreas consisted of sheets of a polygonal-cell carcinoma. In places all gradations between pancreatic acini and tumor cells could be seen, and it was this histologic feature which most strongly supported the diagnosis of primary pancreatic carcinoma.

The histologic appearances of the uterine and thyroid metastases were similar to those of the primary pancreatic neoplasm.

## DISCUSSION

Consideration of these 4 cases, and of the many others reported in the literature, shows that carcinoma of the pancreas is often clinically silent until metastases have occurred. The condition was diagnosed

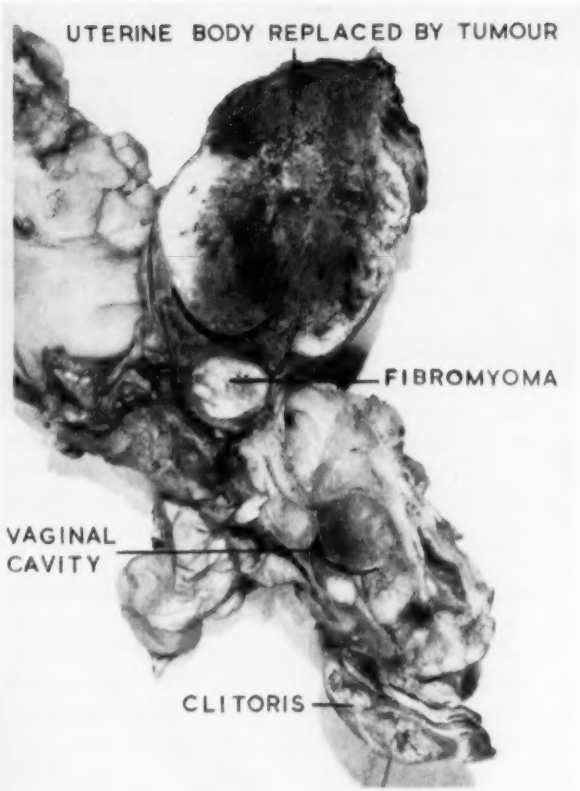


*Fig. 4.* **Sagittal section, through uterus, vagina and clitoris to show secondary deposits.**

correctly in only 26 out of 132 cases reviewed by Berk.[1] Among the factors thought to be responsible are the inaccessible position of the gland, the vague and inconstant functional disturbance produced by neoplasms in the body and tail, and the rapidity with which metastasis occurs. D'Aunoy *et al.*[4] give the average duration of illness at 4½ months, and other workers agree with this figure

Case 1 (T. C.) illustrates the fact that even in the head of the gland a small neoplasm may give rise to secondary deposits in other organs before involving the common bile duct. In some cases of carcinomatosis a primary pancreatic carcinoma might escape detection at necropsy because the head of the gland is incompletely dissected from the con-

cavity of the duodenum. A mass of enlarged lymph nodes containing deposits of tumor around the pancreas may focus attention on the gland but it may be difficult both macroscopically and histologically to determine whether the tumor in these nodes is derived from the pancreas or from some other organ.

Metastases occur not infrequently in the lungs in cases of pancreatic carcinoma[8-11, 13] (1939), and less often in the tracheobronchial and hilar lymph nodes.[8-10] Secondary deposits in the lungs without mediastinal lymph node involvement, as in Case 1, may be explained by venous spread from the liver,[8] whilst spread via the thoracic duct is said to account for the occurrences of hilar node enlargement. The clinical diagnosis of bronchial carcinoma in such patients may be apparently confirmed by the finding of neoplastic cells in the sample of sputum or bronchial aspirate (See Fig. 1), for it is doubtful whether it is possible to decide microscopically whether the cells are derived from a primary or metastatic lung tumor.

On histologic grounds alone metastatic pancreatic cancer in the lung may closely resemble adenomatosis.[15] In both conditions acini of columnar cells are present throughout the lungs, and the hilar lymph nodes may be normal. It is essential in the diagnosis of pulmonary adenomatosis to exclude a primary neoplasm elsewhere. Metastatic carcinoma of the pancreas is unlikely to cause confusion in this context, because however small the primary in the head of the gland, the regional lymph nodes are usually involved. Nevertheless, and even in young subjects, carcinoma of the pancreas must be considered when a pulmonary neoplasm has unusual features.[7]

Squamous carcinoma of the pancreas is an uncommon histologic type. Franco reports one case and quotes McGee. The growth may possibly arise from duct epithelium which has undergone squamous metaplasia. Case 3 illustrates this type of tumor. In this patient squamous carcinoma was found at autopsy in a supraclavicular lymph node (see Fig. 2). Had this node been removed during life, a diagnosis of bronchial carcinoma would have been a reasonable one.

Case 4 illustrates the difficulties encountered in both the macroscopic and microscopic diagnosis of pancreatic carcinoma. The diagnosis made clinically, by biopsy (see Fig. 3), and at autopsy was carcinoma of the uterine body. However, histologic examination of the pancreas showed all stages in the gradation from normal pancreatic acini to primary carcinoma, and it was on these grounds that the final diagnosis was made. Boysen *et al.* have reviewed the occurrence of metastatic

deposits in the uterus. They found only 2 cases, one of which was their own, in which there were secondary deposits of pancreatic carcinoma of this organ.

Metastatic carcinoma of the pancreas should therefore be considered when a new growth has unusual clinical features.

## SUMMARY

Four cases of carcinoma of the pancreas are reported with metastases in the lungs in 2 and in the uterus in 1.

In 2 cases the primary clinical diagnosis was carcinoma of the bronchus and in 1 case carcinoma of the body of the uterus.

In 1 case a uterine biopsy was compatible with the diagnosis of uterine carcinoma and in another case a bronchial aspirate contained malignant cells.

These cases show that metastatic deposits from a primary pancreatic carcinoma may closely simulate carcinoma in other organs.

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# CLINICAL NOTES

## PEPTIC ULCERATION IN PULMONARY EMPHYSEMA

Frank L. Apperly, M.D.

THE ACIDITY of the gastric contents following a standard test meal has been shown to vary with the carbon dioxide ($CO_2$) content of the fasting blood. This statement holds true when many individuals are compared;[1] when the blood $CO_2$ is experimentally raised or lowered in any one individual;[2] and in those diseases which bring about variations in blood $CO_2$.[3]

In 1926 Sundström[4] showed that people living in tropical climates developed a mild hyperpnea, resulting in some alkalemia and a lower blood $CO_2$. Since high gastric acidity is believed to be at least one of the factors responsible for the formation of peptic ulcers, it seemed likely that, other factors being equal, peptic ulcers would be less common in hot climates and, presumably, more common in cold climates. In a survey[5] of the distribution of peptic ulcer in Australia (a country occupied by a people of uniform stock and dietary habits), I found that this was true, the incidence of peptic ulcer per 1000 hospital beds per year in the various state capitals and other cities along the eastern seaboard varying almost uniformly with the latitude from 28 in Mackay, Northern Queensland (latitude 21° 10′S), to 135 in Hobart, Tasmania (latitude 43° 0′S).

From this we might logically expect a high incidence of peptic ulcer in large-lunged ("hypertrophic") emphysema, a disease in which there is often considerable retention of $CO_2$ in the blood. Although I found a few such cases in my own autopsy material, I was not able to establish such a relationship, chiefly because of certain difficulties in interpretation of many of the older records. A search of the literature also revealed nothing helpful until recent years.

In 1952 Green and Dundee,[6] from an examination of 700 consecutive autopsies in males, found that peptic ulcer was approximately three times as frequent in those with emphysema (19 per cent) as in the group as a whole (6.4 per cent). This report also included 72 living

From the Pathology Department, Medical College of Virginia, Richmond, Va.

patients with "chronic pulmonary disease," of whom 14 (19 per cent) had ulcer.

In 1955 Weber and Gregg[7] described 70 patients with benign gastric ulcer, of whom 43 per cent had "chronic lung disease . . . characterized by diffuse lung damage, especially emphysema and fibrosis and accompanied by long-standing symptoms of respiratory dysfunction," concerning which Lowell[8] commented "though not described in detail, (they) appear to have been, in the main, what we are calling chronic obstructive emphysema." A control group of nonulcer patients, of similar age, showed only 10 per cent with comparable pulmonary disease.

In 1956 Lowell *et al.*[8] published the results of a careful examination of 25 cases of pulmonary emphysema (19 men and 6 women, aged 51–81) all heavy cigarette smokers: 6 had peptic ulcer and 3 had bronchogenic carcinoma. At a recent meeting in Boston Lowell's figures had been raised to 40 cases of emphysema with 10 peptic ulcers.[9]

Fig. 1 has been redrawn from a schema by Lowell[8] in which he attempted to correlate tension ("a constellation of emotional states and habits ordinarily attributed to those who are anxious, frustrated, ambitious . . ."), heavy cigarette smoking, emphysema, and peptic ulcer. To his scheme I have added the factors "retention of blood $CO_2$" and "high gastric acidity."

It will be noted that Lowell has also included bronchogenic carcinoma in his schema. In this he is supported by a still more recent publication by Bogardus and Gustafson,[10] who described 31 cases in which

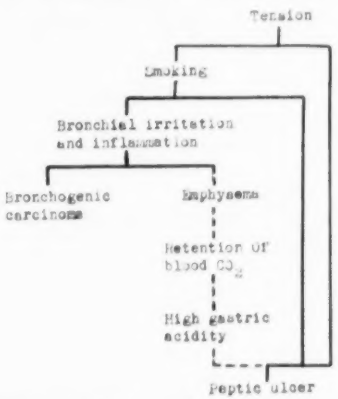


***Fig. 1.*** **Schema correlating tension, smoking, emphysema, and peptic ulcer. Dotted lines indicate factors added by the author to original schema of Lowell *et al.*[8]**

gastroduodenal ulceration was found complicating other diseases, which they attribute to the stress of the latter, acting through the hypothalamus-vagus-pituitary-adrenal cortex axis. Although they make no comment on the point, 7 of these cases (22.6 per cent) had bronchogenic carcinoma.

The verification of our predictions concerning the distribution of peptic ulcer in Australia and its apparently high incidence in certain chronic lung diseases would seem to be further evidence favoring the role of high blood $CO_2$ in the production of high acidity and peptic ulcer.

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# *MEDICAL GRAND ROUNDS*

**E. Clinton Texter, Jr., M.D., *editor***

Report of a weekly Medical Grand Round held at the VA Research Hospital, Chicago, Illinois. These rounds are conducted by Craig W. Borden, M.D., Chief of Medicine, and presented by staff members of the VA Research Hospital. They are participated in jointly by the faculty and clinical clerks of Northwestern University Medical School and guests.

# *Ulcerative Colitis*

**Dr. Craig W. Borden:** Dr. Hines, will you present the first case?

**Case 1**

**Dr. David Hines:** This first patient is a 31-year-old truck driver admitted to this hospital complaining of bloody diarrhea, abdominal pain, and weight loss of approximately 6 weeks' duration. The patient had had a similar episode in 1951 and was told he had an irritable bowel. The patient was well during the interim. It is interesting to note that prior to both of these onsets of symptoms the patient had had extreme emotional upsets. The first concerned his father-in-law who became insane, and the second the death of his mother.

In addition the patient is very discontent with his job, discontent with Chicago and urban life in general. He longs to go back to the country.

Physical examination on admission revealed a well-developed, well-built, well-nourished white man who appeared chronically ill. Hemogram showed a white blood count of 15,400 with a normal differential, hemoglobin of 12.6 Gm., and hematocrit of 37. The sedimentation rate was 50 mm./hr., which subsequently declined to 32 mm. Barium enema and proctoscopic examination showed changes consistent with early ulcerative colitis.

He was treated with a low-residue diet and sulfapyridine, which resulted

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Dr. Joseph H. Stickley and Miss Junko Ikeya assisted in the preparation of the conference.

in nausea and vomiting. He was placed on salicylazosulfapyridine and responded well. Repeated proctoscopy prior to discharge showed marked improvement. At the present time he is asymptomatic. Dr. Cailleteau will show the x-rays.

**Dr. Giles Cailleteau:** On the films taken in June, 1951, the filled colon appears essentially normal. However, on the postevacuation film there is a raggedness to the mucosal pattern and outline of the bowel in its distal one half. If you follow the margins closely, you see very fine serrations.

In the enema done at this hospital the minimal changes are again outlined. There is a fine serration to the outline of the descending and sigmoid colon. On the spot radiographs, this same finding is present in the splenic colon and even in this portion of the transverse colon, so this has the appearance of an early ulcerative colitis.

[The patient was brought into the room.]

***Interview***

DR. E. CLINTON TEXTER, JR.: How are you getting along at the present time?
PATIENT: Just fine.
DR. TEXTER: How many bowel movements are you having a day?
PATIENT: One.
DR. TEXTER: Any blood or cramping?
PATIENT: No.
DR. TEXTER: What about your weight?
PATIENT: I gained between 15 and 20 pounds.
DR. BORDEN: What type of work are you engaged in since you left the hospital?
PATIENT: I am back with the same firm but I am doing dock work now. I explained how the driving was affecting me and they were very nice about it and said they would try to make arrangements to put me some place where it wouldn't bother me.
DR. BORDEN: You put in an eight-hour day, do you?
PATIENT: Yes.
DR. BORDEN: Do you do the work sitting or standing?
PATIENT: Mostly standing, walking around.
DR. TEXTER: What are your plans?
PATIENT: Well, I was planning on getting out of the city and going to California, but then I don't know how that is going to work out.
DR. TEXTER: Thanks very much for coming in [patient was excused].

**Case 2**

**Dr. Joseph H. Stickley:** The next patient is a 38-year-old white male whose illness began in 1946, when there was a gradual onset of mild abdominal discomfort over a 3-week period, accompanied by two to four mushy, bloody stools per day. He was hospitalized and a diagnosis of chronic ulcerative

colitis was established by x-ray and proctoscopic examinations. He recovered slowly and remained asymptomatic until 1950; from 1950 to 1953, he had several moderately severe exacerbations of his disease, each one always preceded by an emotional stress in his domestic or vocational activities. In 1953, he was hospitalized during a severe episode, and after two weeks of cortisone therapy he developed hematemesis and signs of pyloric obstruction. A bleeding duodenal ulcer was found at surgery, and a subtotal gastrectomy was done. During the next few months he continued to have mild bloody diarrhea intermittently and lost 40 pounds in weight; in addition, he developed arthritis in the left hip. He improved during the early part of 1954, was free of symptoms, and gained weight. In May, 1954, after many weeks of working under conditions distasteful to him—also, his wife was pregnant during this time—he had a sudden emotional outburst followed immediately by a severe exacerbation of symptoms; three weeks after the last onset, he was admitted to the VA Research Hospital.

His past history included acute glomerulonephritis as a child. He was always indecisive, submissive, and was never known to ventilate hostilities. He was the one in the family "who was always trod upon."

On admission to the hospital, the patient was poorly nourished, weak, and pale and appeared to be in mild distress from a chronic illness. The left lower quadrant of the abdomen was moderately tender to palpation. Bright red blood was found in the rectum. Granular bleeding mucosa typical of chronic ulcerative colitis was found on proctoscopy. On admission, the hemoglobin was 9 Gm. and dropped to 6.5 after two weeks; the total serum protein was 7.6 Gm. and fell to 3.4 Gm. in two weeks. He received the usual supportive measures plus intramuscular Terramycin with very little benefit. Salicylazosulfapyridine, 1.5 Gm. six times a day, was tried, but the patient became nauseated and refused medication. He became steadily worse, and despite the history of duodenal ulcer, it was thought that cortisone and ACTH should be tried; during the first four days of this therapy, there was great subjective improvement, but on the fifth day the patient had a massive rectal hemorrhage and went into shock. An emergency colectomy was performed. Study of the surgical specimen showed the mucosa of the colon to be totally replaced by ulcerations and pseudopolyp formation. The patient's postoperative course was stormy, with the development of peritonitis, subphrenic abscess, and a pleural effusion on the right side. He recovered slowly, and at the time of discharge from the hospital, 5½ months after admission, his weight was 142 pounds as compared to 116 pounds, the lowest weight during his hospital stay, and to 158 pounds on admission. After discharge from the hospital, he continued to do very well except for some chocolate-colored mucoid drainage from the distal stump of the colon.

**Dr. Frederick W. Preston:** I saw him about two months ago and he now weighs about 160. He is back at work and getting along very well, but he still has an

ulcerative distal colon. We were very reluctant to operate because of limited experience with colectomy in patients who had a previous gastric resection, but this patient has gained weight, and since he was here we have followed other patients with gastric resections and colectomies.

### Comment

**Dr. Texter:** The two patients presented this morning illustrate many of the facets of this fascinating disease, ulcerative colitis. The first patient had a relatively mild disease and responded well to the usual measures plus the addition of Azulfidine. It is of interest that his disease became evident at the time of the period of emotional stress.

The second patient is even more interesting. Doctor Stickley has referred to his personality, which appears to be definitely related to his disease as a precipitating factor. Prior to his admission here, he had a severe emotional blow-up and threw a test tube to the floor. He went home and immediately thereafter had the passage of frequent bloody stools.

The relation of his ulcer to his ulcerative colitis is interesting. The combination of ulcer and ulcerative colitis is rare. It is probable that his ulcer has a strong causal relationship to his previous treatment with cortisone. It came on during the third week of treatment, which is the usual time for ulceration to occur in patients on steroid therapy. I am quite surprised at the rapid course of his ulcer; nonetheless, it is well documented in his previous hospital records.

His course was that of a patient with serious-to-fulminating disease. He showed no response to antibiotics or Azulfidine and a very brief temporary improvement during the four days of ACTH and cortisone. With the onset of massive hemorrhage, there was no choice but to recommend emergency surgery. In retrospect, it probably would have been wiser to operate sooner, but the patient was adamant in his resistance to surgery.

## FACTORS IN TREATMENT OF ULCERATIVE COLITIS

Now to return to some of the problems in the general management of the patient with ulcerative colitis. The type of treatment recommended is influenced by factors that include the extent of the disease, the presence or absence of complications, and associated pathologic lesions. In order to evaluate the results of treatment, we must know something of the natural history of the disease.

### Etiology

Two etiologic factors have been emphasized—the infectious theory and the psychogenic theory. Another important etiologic factor to be considered concerns the personality of the patient. Groen[1] has characterized ulcerative colitis patients as having a good intellect, being careful, neat, egocentric,

and sensitive with an excessive need for love, sympathy, and affection. Daniels[2] has pointed out that 75 per cent of the patients have an emotional conflict as a precipitating cause of their disease.

It has also been suggested that ulcerative colitis may be related to the collagen diseases.[3] Degeneration of the basement membrane has been observed along with disorganization of the connective tissue. All three of these concepts will be seen to be related to the treatment of this condition.

## Pathology

Classical ulcerative colitis involves the colon and occasionally the ileum, usually having a uniform distribution. The lumen is dilated in ulcerative colitis. The wall of the colon tends to be thin and perforations are common.

In some cases there may be evidence of hepatic injury.[4, 5] Significant abnormalities are present in about three quarters of patients who were studied by needle biopsy of the liver.[6]

The increased frequency of carcinoma of the colon in patients with ulcerative colitis is important. Lyons and Garlock[7] report that the incidence of carcinoma was 3.9 per cent in 226 surgically treated cases of ulcerative colitis. However, in patients with chronic ulcerative colitis for over 12 years, 36 per cent developed carcinoma, and in 16 cases with ulcerative colitis involving the rectum for over 12 years, 43 per cent developed carcinoma. Similar statistics are reported by Kiefer *et al.*,[8] who observed 10 cases of cancer in 226 verified cases of ulcerative colitis. This is 66 times the expected incidence of cancer. It is generally considered unwise to continue to rely on medical treatment for more than 10 years in patients with ulcerative colitis because of the increasing risk of carcinoma.

## Clinical Course

The clinical course of nonspecific ulcerative colitis is extremely variable. Frequently it is impossible to determine when a patient is first seen what is likely to happen during the ensuing months and years. In some patients the disease is mild in the beginning but later may become severe or even fulminating. In other patients remission or clinical recovery may follow a severe attack.

Evaluation of any specific therapy is impossible without taking into consideration the variable clinical course of the disease including its spontaneous remissions. Bone *et al.*,[9] reporting on the Duke University Hospital series of 112 patients who had been followed for one year or longer, noted that patients followed one of four clinical courses. The majority of patients (55 per cent) had repeated attacks with recovery between attacks. Thirty per cent of patients showed improvement between attacks, while 10 per cent had continuous symptoms and 5 per cent followed a fulminating course. The outlook

was more favorable for those whose initial symptoms were mild, whose disease was limited to the left side of the colon; a less favorable course was taken by the very young and the very old and those who had either segmental, right-sided, or universal involvement as shown by x-ray. Ricketts *et al.*[10] in correlating the clinical course of the disease with the x-ray findings, in a series of 156 patients, found that 16 patients (10 per cent) showed regression in the radiologic appearance, 39 (25 per cent) showed progression, and 101 (65 per cent) showed no change.

## MEDICAL TREATMENT

The useful therapeutic agents for ulcerative colitis can be divided into three categories: (1) the antibiotics and sulfonamides, (2) corticotropin, cortisone, and similar steroids, and (3) psychotherapy. No attempt will be made to discuss adequately the various aspects of psychotherapy. It is important to point out, however, that the administration of a therapeutic agent *ipso facto* is a psychotherapeutic influence also. In a disease such as ulcerative colitis the person who administers the drug is frequently more important than what drug is administered.

### Diet and Control of Diarrhea

It is customary to use a high-carbohydrate, high-protein, low-fat, low-roughage diet. However, this may have limited value in managing the severely ill patient. Nonspecific agents to check the diarrhea may be employed as well as retention enemas containing various medications.

### Antibiotics and Sulfonamides

Machella[11] summarized the status of sulfonamides and antibiotics in 1952, noting that good results of treatment were reported in 57.7 per cent of 1275 cases treated with sulfonamides, whereas improvement was reported in 61.6 per cent of 167 patients treated with a variety of antibiotics. Since that time, however, the antibiotics have been used with less frequency, and interest has centered more on the sulfonamide salazopyrin. Salazopurine (Azulfidine) is the result of diazotization of para-aminosalicylic acid with sulfapyridine. Bargen terms Azulfidine to be the most valuable drug to be introduced in the treatment of ulcerative colitis. His opinion is shared by other authorities, although there is little statistical support for this opinion.

Morrison compared the results of treatment in a series of 47 patients treated with Azulfidine with results in another series of 60 patients used as a control series.[12] These two groups were not treated simultaneously, however. Morrison reported that 18 per cent of the patients in the Azulfidine series were symptom-free and 52 per cent were improved, as compared to 5 per cent symptom-free and 32 per cent improved in the control series. Svartz[14] points out that

Azulfidine has been shown to have a marked affinity for connective tissue, and particularly for tissues rich in elastin. Of 124 patients treated with salazopyrin and accounted for up to 1944, 90 had shown improvement.

During the past three years, an attempt has been made, using the double-blind approach, to assess the value of Azulfidine as compared to sulfapyridine and placebo in the management of patients with ulcerative colitis.* Twenty-six patients were started on one of the drugs in random fashion and were followed for 6 months–2½ years. Of the 13 patients who received Azulfidine, 10 improved, 2 showed no change, and 1 became worse. Of the 6 patients who received placebo, 3 improved, 1 showed no change, and 2 became worse. Of the 7 patients who received sulfapyridine, 2 improved, 1 showed no change, and 4 became worse. These findings are similar to those obtained by others with salazopyrin. It would appear that Azulfidine is of most value in the mild-to-moderately ill patient but has little effect upon the course of patient with severe or fulminating ulcerative colitis. No serious evidence of toxicity was noted from Azulfidine in the present study. Periodic white blood counts were performed, and this would appear to be a good practice, as fatal agranulocytosis developed in a patient who had been treated previously with Azulfidine.[15] The causative agent could not be stated with certainty, as he had received other drugs.

### Corticotropin, Cortisone, and Other Adrenal Steroids

In 1951 Kirsner and Palmer[16] reported on 41 patients treated with ACTH. Clinical response during administration of the corticotropin was considered good in 27, moderate in 7, slight in 2, and nil in 4 patients. Administration of large quantities for 6 or 8 weeks was more effective than short periods of treatment.

Long-term treatment of ulcerative colitis with corticotropin has been advocated. Wirts *et al.*[17] reported that among 49 patients relapses following a course of hormone therapy occurred in 16 during the early period, and in 12 patients 12–18 months after initial hormone therapy. Repeated treatment with corticotropin brought about improvement less prompt and less complete than that obtained initially.

Other investigators are less enthusiastic about the value of ACTH in the treatment of ulcerative colitis. Perforations have been reported to follow its use.[17-19] Deep undermined ulcers following discontinuance of ACTH therapy[19] developed in 5 of 16 patients receiving ACTH or cortisone, and in 1 patient who refused surgery they were accompanied by a fatal perforation. The deep undermined ulcers are more common in those patients having a short

* The drugs were supplied by L. A. Elwinger, Pharmacia Laboratories, Rochester, Minn.

course without significant fibrosis of the bowel wall. Approximately half of patients treated with ACTH initially are improved and in a few instances the remission may be a lasting one. However, about 80 per cent of patients with relapse, recurrence occurs and in general this tends to be more severe than the initial bout of the disease. Cortisone has been found less effective than ACTH in inducing a remission.[19]

With the passage of time, most workers have become less enthusiastic about the use of ACTH and other steroids in the treatment of ulcerative colitis. Bargen[12] limits the use of hormones with ulcerative colitis to patients who have complications of ulcerative colitis including arthritis, uveitis, and pyoderma gangrenosum. We have had some experience with the newer steroid compounds, but this is not sufficient to attempt evaluation at this time.

There is no question that ACTH and the adrenal steroids are potent therapeutic agents in the use of ulcerative colitis. The mechanism of their action is not known but biopsy studies have shown restoration of the basement membrane toward normal and improvement in the histologic appearance of the connective tissue following administration of ACTH.[20]

## Indications

### *ACTH*

One generally accepted indication for the use of ACTH is in patients with fulminating disease for whom surgery is indicated. Formerly, the mortality rate of ileostomy in this group of patients exceeded 20 per cent but with the use of intravenous ACTH, Lahey reported a mortality of ileostomy in the severely ill patient[21] as only 2 per cent. The other indications for the use of ACTH have not crystallized. Some use hormones in the majority of patients. I prefer to limit its use to the severely ill patient to whom you have little else to offer besides colectomy. Some of these people may develop a remission. If they do not, at least they usually improve so that they are better candidates for surgery.

### *Combination Therapy*

In the pre-ACTH and Azulfidine era, Kiefer[22] reported that in 327 patients medical management was satisfactory in 46 per cent and unsatisfactory in 54 per cent, while 36 per cent of the patients came to operation. It appears probable that there has been improvement in the medical management of ulcerative colitis with the use of Azulfidine and steroids in selected cases. Azulfidine is mainly of value in the mild to moderately ill patient. ACTH given by the intravenous route is of most value in the fulminating patient. A combination of therapy according to the individual circumstance would then be employed for patients with moderately severe disease. Parenteral penicillin and strepto-

mycin should be administered concurrently with ACTH therapy. There appears to be little use for any of the other antibiotics.

**Dr. Borden:** Very good.

One of the problems illustrated by Case 2 has to do with the surgical management and indications for surgery. Do you care to say a word about that, Dr. Preston?

## SURGICAL TREATMENT

**Dr. Preston:** Ulcerative colitis is usually a medical disease, but about 15 to 20 per cent of the patients have complications including pseudopolyposis, carcinoma, fistula formations, severe hemorrhage, rectal fistulas and abscesses, and then pyogenic dermatitis, all of which require surgery.

The surgical procedures used have become fairly well standardized in the last ten or fifteen years with the exception of the very severe fulminating type of case, which remains a problem. An ileostomy is life-saving, yet the patient may not really improve until the diseased portion of the colon is resected. Colectomy may be impractical because it carries too high a risk in patients that are as sick as these patients are. Therefore, one must compromise.

For other patients with ulcerative colitis, we now attempt to do an ileostomy and a total colectomy and resection of the rectum at the same time. There are some patients in which the entire colon with the exception of the rectum has been removed. It would be very nice if there would be some medical treatment that could be introduced that would enable those patients to have the ileostomy taken down so they have a gastrointestinal continuity. Some of those patients have had another operation in which the ileum was anastomosed to the remaining stump of the rectum, but invariably the disease activates again in the remaining part of the rectum.

**Dr. Borden:** In ulcerative colitis the internist may be a little slow in calling the surgeon in. The patient in Case 2 was losing weight and was toxic and febrile. In retrospect, the proper time to operate was between the seventh and tenth day. This was proposed to him and he didn't accept it. He had an irreversible disease and he would not have been such a poor operative risk had he been operated on in the first week.

This does not apply to 80 per cent of the patients, who will respond to medical management and conservative regimens. The distinguishing features are the response of the fever curve, the weight, and the over-all health; these will indicate whether the disease is progressing upward or veering downward. And I would like to urge the internists to be a little more aggressive in dealing with these fulminating situations.

We do plan later on to have a continuation of our psychosomatic sessions on the dynamics of patients of ulcerative colitis, but I think maybe we could

profit by at least some words now. Dr. Whitman, do you want to make a few comments?

## PSYCHOLOGIC ASPECTS

### Personality Features

**Dr. Roy Whitman:** An experiment I heard about the other day might be interesting in connection with a few things Dr. Texter said. It is called a level-of-aspirations test, in which psychologists used a small pinball machine, and the subject was to estimate the score that he was going to make each time. They studied ulcer patients, ulcerative colitis patients, and hospital people who were in a so-called normal category. The results were rather interesting.

The ulcer patient would get a score, let's say, of 25, and was asked then to estimate how well he could do the next time. Invariably he would say 30 or 35—he would always push his aspiration level a little bit higher. The normal control group would often estimate their score a little bit higher, or a little bit lower, but stay within a much narrower range.

In contrast, the ulcerative colitis group consistently rated themselves lower. If they got a score of 25 and they were asked to predict how they would do the next time, they would say 20. If they dropped then they would still go lower. And even if they maintained a score of 25 or 30 over three or four times, they would still always predict 20 or 22.

I think this illustrates the point you made—that socially this group is not among the successful businessmen or executives, such as we often see in the peptic ulcer group.

### Therapeutic Considerations

It is difficult to evaluate therapy. How much is the drug effect and how much is placebo effect? Usually 35 to 50 per cent is placebo effect and I think Dr. Texter came up with something like that, so any time you evaluate a disease with the general typical characteristics of a remitting or chronic disease, you should subtract 35 to 50 per cent from the effect of the drug you are using.

This is a psychogenically caused illness. But I think it is a psychosomatically triggered illness with an emotional process that sets it under way.

I had the opportunity of interviewing the patient in Case 2 once. We talked for a while and he told me the story of his recent episode, which was quite a dramatic one as you pointed out, as going into a peak of rage and throwing the test tube down, having previously suffered a good deal of insult by another person who worked in the laboratory. And as he was telling the story, he became emotionally immersed in the story and immediately started to have cramps and had a bloody stool. This sort of reaction is a very difficult problem with this type of patient, because it is almost as though he were so emotionally attuned to this type of emotional stress that just talking about it short-circuited to the bowel. After the interview, he asked that I not

see him again, because he recognized this factor. The physician who handles the case directly should handle the psychotherapy. Most people recommend a relatively superficial and directive type of psychotherapy. In going over these peoples' life situations, you can say, "Why don't you avoid this type of situation or do this in a certain way—," because the thing you want to avoid with these people is stress.

### Alternation with Psychosis

If we would make a hierarchy of psychosomatic disease, the ulcer would be at the top, but I think at the lowest end of the scale would be the ulcerative colitis patient. This particular illness is associated with the highest percentage of alternation with actual psychosis. A friend of mine at the Institute for Analysis was talking to a psychotic patient when the patient came out of the psychosis, said, "I feel normal now," and started to have bloody stools. My friend was struck by the remarkable substitution of the two processes—the psychosis for the ulcerative colitis.

## GENERAL DISCUSSION

**Dr. Reuben Wasserman:** In respect to this question of alternation between psychosis and symptoms of ulcerative colitis, how frequent do you find psychosis following colectomy?

**Dr. Whitman:** I have had a chance to see only two patients with colectomies. Even though the people are very anxious in social life and afraid of soiling and letting loose gas, by and large they do well psychiatrically. This is an important thing to consider when one makes the early decision that should be made for surgery, because very often the decision will be postponed on the basis the patient says, "My God, how will I feel with an opening in the abdomen!" And the doctor says, "What a terrible thing to carry around!" In many ways it is unpleasant, but it is not that bad.

**Dr. Everett Shockett:** If there is any question about whether one can do as well medically as surgically in treating acute fulminating cases in the initial attack, there are two other factors that favor the medical approach. When you take the patient that has never been sick before and do a colectomy, you have much more difficulty. When he has been sick for a long time, you are eliminating a handicap and his reaction is better.

It is my impression many of the carcinomas develop in the people who are not cured, but are clinically well enough to carry on their own way of life. This presents quite a problem.

**Dr. Texter:** The incidence of carcinoma is confused. The literature cites an increased frequency, yet in the series of 110 patients at Duke University Hospital only 1 patient developed carcinoma. However, many people feel that colectomy is indicated for the young patient who had disease for longer than 10 years.

Some people won't consent to surgery, and if the patient won't consent you can't operate on him. I saw one woman who refused surgery, put herself on a tea-and-toast diet, and had fewer stools and said she was getting better. At autopsy she had a massive perforation involving the entire colon.[19]

In certain cities there are "ileostomy clubs," which can be a great aid. Patients talk over their problems. It is significant that all the bags and appliances in use have been designed by patients.

**Dr. Robert P. Gilbert:** What are the current ideas about the mediation of the ulcerative process from the brain to the colon?

**Dr. Texter:** That is the missing link.

**Dr. Borden:** Lysozyme has been discredited.

**Dr. Texter:** Lysozyme is the result of ulceration rather than the cause.

**Dr. Borden:** One thing you have to remember is that there is a mortality with acute ulcerative colitis.

**Dr. Shockett:** Those patients have a surgical mortality, too.

**Dr. Borden:** That is true, particularly if you delay. There was a classmate of mine in medical school who died on the tenth day of his disease. It was a difficult case, and when the problem of surgery came up the decision to operate was not made in time to save him.

**Dr. Preston:** I don't think ileostomy should be such a great shock to the patient.

**Dr. Borden:** Isn't it true most patients with modern ileostomies are pleased and adjust very well to the ileostomy? It is my experience they get along well.

**Dr. Shockett:** Unless they have an acute fulminating case, they don't have the time to make the adjustment.

**Dr. Borden:** Not if they are dead.

**Dr. Wasserman:** One point should be made regarding ileostomies which the surgeon should take into account. Certain areas on the abdomen are easier to fit with the bag. The doctor should consult with the person who will make the bag, who knows more about the problems of fitting the bag.

**Dr. Shockett:** Getting back to the carcinoma, don't you agree that the incidence of carcinoma increases if the disease is burned out? These young people are bound to live ten years more and you are almost confronted with the conclusion maybe we should do earlier surgery for prophylaxis against cancer.

**Dr. Preston:** Patients with carcinoma usually have pseudopolyps. The ones with the pseudopolyps should be operated on. That is only about 18 per cent of the total number of patients of ulcerative colitis.

**Dr. Gene Stollerman:** What do you think of the effect of Azulfidine? How do you explain it?

**Dr. Texter:** No good fundamental work has been done on this. Dr. Svartz originally proposed use of Azulfidine, and she felt the compound localized in connective tissue. Further study is necessary.

## SUMMARY and CONCLUSIONS

The principles underlying treatment of chronic ulcerative colitis have been reviewed.

- Psychotherapy, use of corticosteroids, and antibiotics and chemotherapy are the most useful adjunctive measures in addition to general treatment.
- ACTH is the most satisfactory agent for treatment of severe disease. However, approximately 80 per cent of patients treated ultimately will relapse.
- Azulfidine is mainly of value in the mild to moderate cases.
- Medical management can achieve reasonably satisfactory results in 50–75 per cent of patients with ulcerative colitis.
- Surgical treatment will be necessary in 25 per cent of patients.

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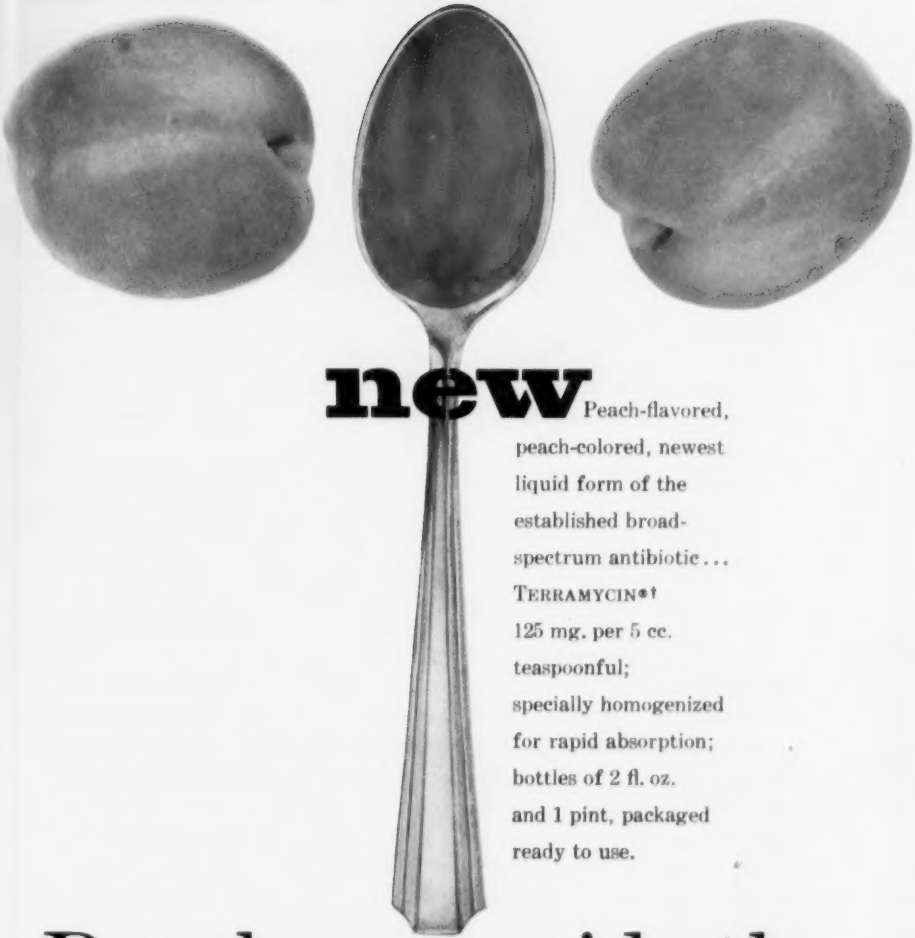

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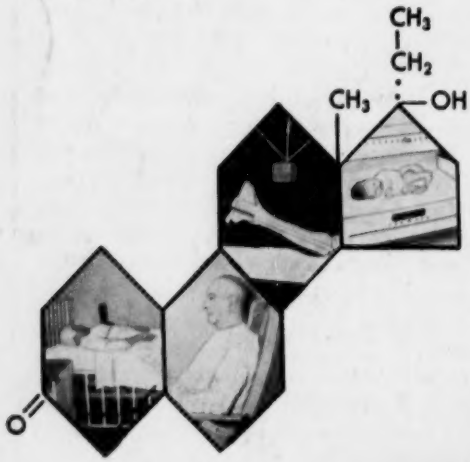


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